IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC., Plaintiff, v. MSN LABORATORIES PRIVATE LIMITED and MSN PHARMACEUTICALS, INC, Defendants.	C.A. No. 22-cv-228 (RGA) (JLH) (Consolidated)

DEFENDANTS' OPENING POST-TRIAL BRIEF ON INVALIDITY

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TABLE OF ABBREVIATIONS

Term	Definition
'015 patent	U.S. Patent No. 11,098,015 (JTX-003)
'349 patent	U.S. Patent No. 11,298,349 (JTX-004)
'439 patent	U.S. Patent No. 11,091,439 (JTX-001)
'440 patent	U.S. Patent No. 11,091,440 (JTX-002)
1-1 impurity	6,7-dimethoxy-quinoline-4-ol
API	Active pharmaceutical ingredient
Berge	Berge et al., Pharmaceutical Salts, Journal of Pharmaceutical Sciences, 66, 1-19 (1977) (DTX-166)
Brown	International Publication No. WO 2010/083414 A1, to Brown et al. (DTX-291)
Bighley	Bighley et al., Salt Forms of Drugs and Absorption, in 13 Encyclopedia of Pharmaceutical Technology 453 (James Swarbrick & James C. Boylan eds., 1995) (DTX-167) ("Bighley" is a chapter in the "Swarbrick" encyclopedia)
Cabozantinib I Case	*Exelixis, Inc. v. MSN Lab'ys Priv. Ltd.*, No. CV 19-2017-RGA-SRF (D. Del.)
DTX	Defendants' Trial Exhibit
Exelixis	Plaintiff Exelixis, Inc.
FDA Guidance	FDA, Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, Center for Drug Evaluation and Research (February 1987) (DTX-170)
FDA GTI Guidance	FDA Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommend Approaches (DTX-091)
Gibson	Steele, Preformulation Predictions from Small Amounts of Compound as an Aid to Candidate Drug Selection, A Practical Guide from Candidate Drug Selection to Commercial Dosage Form (2001) (DTX-392)
Girindus	Girindus AG Kuensebeck
HCC	Hepatocellular carcinoma
HPLC	High-performance liquid chromatography
JTX	Joint Trial Exhibit
Lachman	Lachman et al., Pharmaceutical Dosage Forms, Second Edition, 1989 (PTX-553, which is a duplicate of DTX-288)

Term	Definition
Malate Salt Patents	Collectively, U.S. Patent Nos. 11,091,439; 11,091,440; and 11,098,015
MSN	MSN Laboratories and MSN Pharmaceuticals
MSN Laboratories	Defendant MSN Laboratories Private Limited
MSN Pharmaceuticals	Defendant MSN Pharmaceuticals Inc.
NCCN	National Comprehensive Cancer Network
POSA	Person of ordinary skill in the art
PTX	Plaintiff's Trial Exhibit
RCC	Renal cell carcinoma
Regis	Regis Technologies, Inc.
Remington's	Remington's Pharmaceutical Sciences Handbook (e.g., DTX-284)
Stahl	Stahl & Wermuth, "Monographs on Acids and Bases," in Handbook of Pharmaceutical Salts: Properties, Selection, and Use 10 (Stahl, P.H., Wermuth, C.G., eds., 2002) (PTX-610)
Swarbrick	Swarbrick et al., Encyclopedia of Pharmaceutical Technology (e.g., PTX-394)
Tong	Tong et al., In situ Salt Screening—A Useful Technique for Discovery Support and Preformulation Studies, Pharm. Dev. Technol. 3 (2), 215-223 (1998) (DTX-243)
TKI	Tyrosine kinase inhibitor
Vippagunta	Vippagunta et al., Crystalline solids, Advanced Drug Delivery Reviews, 48, 3-26 (2001) (DTX-191)

I. INTRODUCTION

Exelixis will continue to enjoy patent protection over cabozantinib until 2026. Unsatisfied with its original patent term, Exelixis has attempted to extend its patent monopoly—and the monopoly profits that come with it—by obtaining additional patents covering things Exelixis did not actually invent, already received patent coverage for, or that are obvious applications of the prior art. At trial, MSN showed by clear and convincing evidence that the asserted claims of the Malate Salt Patents[1] are invalid for lack of written description and obviousness-type double patenting and that the asserted claim of the '349 patent is invalid as obvious.

The asserted claims of the Malate Salt Patents are generally directed to crystalline (L)-malate salts of cabozantinib. The claims broadly cover *any and all* such salts, i.e., *any and all* crystalline forms of cabozantinib (L)-malate. Indeed, the trial record revealed that there are at least 11 distinct crystalline polymorphs that are presently known, and potentially many more, all of which fall within the scope of the claims. The specification, on the other hand, discloses the undisputed fact that the inventors only possessed two of them, the N-1 and N-2 forms. In other words, the specification does not provide written description support for the full scope of the claims. Exelixis argues that those two forms are representative of the entire breadth of the claimed genus, including MSN's novel Form S. But the evidence at trial showed that individual polymorphs have their *own* unique and unpredictable structures and properties. Thus, Forms N-1 and N-2 are not representative of all species within the scope of the claims and, therefore, do not save the patents from being invalid for lack of written description.

The asserted claims of the Malate Salt Patents are also invalid for obviousness-type double patenting. Exelixis' '473 patent, which was at issue in *Cabozantinib I*, claims pharmaceutically

[1] All defined terms herein are set forth in the Table of Abbreviations on page vi.

acceptable salts of cabozantinib. It was undisputed at trial that crystalline cabozantinib (L)-malate, as claimed in the Malate Salt Patents, is a pharmaceutically acceptable salt. The evidence further showed that a POSA would have been motivated with a reasonable expectation of success to prepare crystalline cabozantinib (L)-malate during a routine salt screen. Any additional claim elements were disclosed in a priority application to the ’473 patent, which was available in the prior art. Thus, there are no patentable distinctions between the claims of the earlier-expiring ’473 patent and the asserted claims of the Malate Salt Patents. Application of obviousness-type double patenting will therefore prevent an improper timewise extension of Exelixis’ patent rights.

Claim 3 of the ’349 patent, directed to formulations of cabozantinib (L)-malate that are essentially free of a particular genotoxic impurity (“GTI”), would have been obvious over the teachings of the prior art. Specifically, the Brown reference disclosed a process for synthesizing cabozantinib (L)-malate that inherently produced cabozantinib API that was essentially free of the claimed GTI. Alternatively, the evidence showed that a POSA would have used a routine recrystallization method to purify cabozantinib (L)-malate and ensure it was essentially free of the GTI. Either way, Exelixis did not meaningfully dispute at trial that incorporating that API into a tablet or capsule with well-known excipients would have been within the skill of a POSA. Indeed, both the ’349 patent specification and Exelixis’ expert conceded as much. The claimed invention is little more than a routine formulation of a known API.

For the reasons presented at trial and below, the asserted claims are invalid.

II. LEGAL STANDARD

A. Lack of written description

To satisfy written description, the patent specification must “clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). Sufficient description of a genus

claim "requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus." *Id.* at 1350.

The standard for what constitutes a representative number of examples will "necessarily vary depending on the context, considering such facts as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology and the predictability of the aspect at issue." *Ajinomoto Co. v. Int'l Trade Comm'n*, 932 F.3d 1342, 1359 (Fed. Cir. 2019). "Evidence showing that a claimed genus does not disclose a representative number of species may include evidence of species that fall within the claimed genus but are not disclosed by the patent, and evidence of such species is likely to postdate the priority date." *Amgen, Inc. v. Sanofi*, 872 F.3d 1367, 1374 (Fed. Cir. 2017).

B. Obviousness

A patent claim is invalid for obviousness "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Whether a patent claim is obvious is a question of law based on four underlying questions of fact: (a) the level of ordinary skill in the pertinent art; (b) the scope and content of the prior art; (c) the differences between the prior art and the claims at issue; and (d) secondary considerations, which are also known as objective indicia of nonobviousness. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966).

"Subsumed within the *Graham* factors is a subsidiary requirement … that a skilled artisan would have been motivated to combine the teachings of the prior art references … [with] a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). A "motivation to combine the relevant prior art teachings … does not have to be

found explicitly in the prior art references sought to be combined, but rather may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." *Id.* at 1362. "[I]nherency may supply a missing claim limitation in an obviousness analysis … when the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020). "Extrinsic evidence," including "non-prior art data" and "the work of the inventor" "can be used as the evidence of inherency." *Id.* at 1329–30.

C. Obviousness-type double patenting

A claim in a later-expiring patent is invalid for obviousness-type double patenting if it is not patentably distinct, i.e., it would have been obvious to a POSA, from the claim in an earlier-expiring reference patent alone or together with the prior art. *See Abbvie, Inc. v. M. & T. Kennedy Inst.*, 764 F.3d 1366, 1374, 1378–79 (Fed. Cir. 2014). The analysis entails two steps: (1) identify the differences between the reference claim of the earlier-expiring patent and the claim of the later-expiring patent, and (2) determine whether those differences render the later claim patentably distinct. *Id.* at 1374. The second step is analogous to an obviousness analysis. *Id.* at 1378.

III. LACK OF WRITTEN DESCRIPTION OF THE MALATE SALT PATENTS

The Malate Salt Patents are a clear example of the broad claim scope overreach that the written description requirement is meant to prevent. "The purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1376 (Fed. Cir. 2009). Here, Exelixis discovered two closely related crystalline forms of cabozantinib (L)-malate with similar properties, Forms N-1 and N-2. For that discovery, Exelixis was granted patents with claims to those forms. But the Malate Salt Patents, which share an identical specification with

Exelixis' earlier patents, claim a much broader genus that includes *any* crystalline form.

At trial, it was undisputed that Exelixis did not invent or possess any other crystalline forms. Written description may only be satisfied, then, if the disclosed species, Forms N-1 and N-2, are representative of the broad crystalline cabozantinib (L)-malate genus. The evidence clearly and convincingly showed they are not. Forms N-1 and N-2 have different crystal structures compared to other forms. And they have different physico-chemical properties, which the experts agreed can present important real-world differences in the pharmaceutical use of these compounds. Because the only two forms disclosed by the specification are not representative of the claimed genus nor sufficient for a POSA to visualize all forms of crystalline cabozantinib (L)-malate, the Malate Salt Patents are invalid for lack of written description.

A. Exelixis did not possess the full scope of the crystalline cabozantinib (L)-malate salt genus.

1. The claims are directed to a genus of all crystalline forms of cabozantinib (L)-malate.

Each of the asserted claims is directed to crystalline cabozantinib (L)-malate. DFF ¶ 31. For a salt to be "crystalline," it *must* have a regular, repeating underlying arrangement of molecules. DFF ¶¶ 18–20. A crystalline salt can exist in multiple unique regular, repeating crystal structures, or polymorphs, and each version is referred to as a crystalline "form" of the compound. DFF ¶ 19. If a material does not have an underlying, repeating structure and instead the arrangement of molecules is random, it is *not* crystalline and is not covered by the asserted claims. DFF ¶ 18–20. These basic scientific facts were not disputed at trial.

While Exelixis makes much of the fact that the word "form" does not appear in the claims, this is a distraction. The claims cover—and indeed require—that the cabozantinib (L)-malate be crystalline, which a POSA would necessarily understand to mean it exists in a particular crystalline form. DFF ¶¶ 20, 31. Exelixis' expert Dr. Trout admitted that the scope of the claims is the same

whether the word "form" is explicitly included or not. DFF ¶ 32.

Thus, there should be no dispute that the asserted claims cover a genus of all currently known or future-discovered crystalline forms of cabozantinib (L)-malate, regardless of whether Exelixis invented them. DFF ¶¶ 31–35. At trial, Dr. Trout suggested that the inventors discovered the most "pharmaceutically relevant" crystalline forms. Tr. 860:7–16 (Trout). But that is not a limitation of the claims. DFF ¶ 33. Nor do the claims require any specific crystalline structure or physical or functional property. Exelixis cannot read in new limitations to retroactively fit the scope of the claims to what it invented as a shield for purposes of written description while simultaneously using the broad scope of the claims as a sword for purposes of infringement.

2. Exelixis only possessed crystalline cabozantinib (L)-malate Forms N-1 and N-2

The "touchstone of written description is possession as of the priority date." *In re Entresto*, 2023 WL 4405464, at *21 (D. Del. July 7, 2023), citing *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1255 (Fed Cir. 2004). While the asserted claims are directed broadly to all crystalline cabozantinib (L)-malate salts, it was undisputed at trial that Exelixis possessed only two crystalline forms: Forms N-1 and N-2. DFF ¶¶ 36, 47. Its 2015 NDA submission to FDA confirmed that "[c]abozantinib [(L])-malate was found to exist in two neat, closely related, crystalline forms (N-1 and N-2) that have similar properties" and that there were "no other forms identified." DFF ¶ 38.

The specification's extensive disclosure of Forms N-1 and N-2 reflects what Exelixis discovered. It provides detailed characterization data, including XRPD, TGA, DSC, and moisture sorption data. DFF ¶ 37. Indeed, this is the same data and specification that supported Exelixis' previously issued patents on each of those crystalline forms. DFF ¶ 39. Were the Malate Salt Patent claims directed only to those forms, there would of course be no dispute; but, having failed in *Cabozantinib I* to prove infringement by MSN on the more narrowly tailored patent claims directed

only to Form N-2, Exelixis has tried again with the same specification but significantly broader claims. Thus, the facts here resemble *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, where having failed to prove infringement on "spike" claims, the patentee asserted "broader" "spikeless" claims that had been prosecuted after introduction of the defendant's product. 558 F.3d at 1378.

But like in *ICU Medical*, where the Federal Circuit held a POSA "would not understand the inventor … to have invented a spikeless valve," *id.* at 1378, the disclosures in the specification cannot bridge the gap between what the inventors actually had and what Exelixis now claims they possessed. Based on the specification, a POSA would know the crystal structure, working examples of manufacturing processes, and physical properties of Forms N-1 and N-2, telltale signs of which forms Exelixis had invented. DFF ¶¶ 37–39, 47–48. In contrast, a POSA would *not* know what other forms of crystalline cabozantinib (L)-malate existed, how to make those forms, what the crystal structure of such other forms might be, or what properties each unknown form would have. DFF ¶¶ 48–54. At trial, Dr. Trout repeatedly conceded that all of this information would be unpredictable based on the disclosures of the Malate Salt Patents. DFF ¶¶ 49–51.

The trial evidence also established that at least *nine* other forms of crystalline cabozantinib (L)-malate have been discovered that Exelixis never possessed, and there may be more. DFF ¶¶ 40–45. Dr. Steed explained how the XRPD diffractograms for each of the 11 reported forms establish that they are each distinct and unique. DFF ¶¶ 41–42.[2] Thus, there can be no question here that the inventors did not possess *all* crystalline forms of cabozantinib (L)-malate.

B. Forms N-1 and N-2 are not representative species of the crystalline cabozantinib (L)-malate salt genus.

[2] While Dr. Trout noted that a comparison of any two of these diffractograms revealed certain overlapping XRPD peaks, Dr. Steed explained how a POSA would look at the entire pattern and see that, despite some overlap, which is expected when performing such comparisons, each overall pattern is unique. DFF ¶¶ 42–43. And of course, in the prior *Cabozantinib I* Case, Dr. Trout accepted the existence of these other forms without dispute. Tr. 915:5–16 (Trout).

1. Forms N-1 and N-2 have different crystal structures and physico-chemical properties from other crystalline forms.

The crystal structures and physico-chemical properties of Forms N-1 and N-2 differ from other crystalline cabozantinib (L)-malate salts. DFF ¶¶ 52–54. Forms N-1 and N-2 are reported to have "improved properties" over the cabozantinib free base and other salts of cabozantinib. DFF ¶ 55. But the specification makes clear that while the names "used herein to characterize a specific form, e.g., 'N-2'" are "used as mere identifiers," the scope of the disclosed crystalline forms was narrowly limited to forms "possessing *similar or identical* physical and chemical characteristics … in accordance with the characterization information presented herein." JTX-0001.36–37.

Exelixis must—and did, at trial—concede that the properties of one crystalline form are not predictive of other crystalline forms. DFF ¶¶ 26, 50, 63. For example, both sides' experts agreed that different crystalline forms of a salt can have different densities, melting points, solubilities, hygroscopicity, vapor pressure, and stability. DFF ¶¶ 56–64. But it is not just theoretical here. The patent literature confirms that each of the 11 reported crystalline cabozantinib (L)-malate salts are prepared in different ways, which is what leads to the creation of their different crystalline structures and resulting different physico-chemical properties. DFF ¶¶ 44—45.

The evidence at trial also provided many examples of differences in properties between known crystalline forms. For instance, the melting points for Form N-1 and N-2 are 187°C and 186°C, respectively. DFF ¶ 56. But those melting points differ (as a POSA would expect) from other crystalline forms, such as Mylan's Form M-4 at 174.87°C and MSN's Form S at 113°C. *Id.* In addition, Forms N-1 and N-2 are non-solvated—that is, they show no solvent loss up to 185°C in a TGA experiment. DFF ¶ 58. By contrast, Mylan's Form M-1 is a solvated crystalline form that shows 4.26% solvent loss, and MSN's Form S is a solvated form where the solvent is water (also known as a hydrate). *Id.* Still further, Forms N-1 and N-2 are both non-hygroscopic, while

MSN's Form S is hygroscopic. DFF ¶ 60. These differences across the board confirm why a POSA would not expect different crystalline forms of cabozantinib (L)-malate to have physical and chemical properties similar to Forms N-1 and N-2. DFF ¶¶ 52, 63–64.

2. The differences between Forms N-1 and N-2 and other crystalline forms reflect a lack of representativeness.

Possession of Forms N-1 and N-2 is insufficient to disclose common "structural features" for all crystalline cabozantinib (L)-malate salts, and the specification fails to identify physical and chemical properties of crystalline cabozantinib (L)-malate salts beyond Forms N-1 and N-2. *Ariad*, 598 F.3d at 1350. The dispute here parallels this Court's analysis in *Entresto*. There, the asserted patent generally related to "combination[s]" of sacubitril and valsartan. 2023 WL 4405464 at *2. The active ingredient in Entresto was a "complex" of those drugs, which is "a single-component material in which multiple types of molecule are linked together in a non-covalent manner." *Id.* at *13. But complexes were not known for use as APIs at the priority date. *Id.* at *16. Thus, a POSA with the asserted patent in hand would not have known of or foreseen that a complex of valsartan and sacubitril would exist. *Id.* at *15. For that reason, the inventors, "by definition, could not have possession of, and disclose, the subject matter of such complexes in 2002." *Id.* at *22.

The same is true here: there were undisputedly crystalline forms of cabozantinib (L)-malate that the inventors did not possess or describe as of the priority date. Exelixis concedes the existence of MSN's Form S, and eight more forms are described in the patent literature, one of which is also claimed in an issued U.S. patent (Mylan's M-4). DFF ¶ 40. But nothing in the Malate Salt Patents' specification would have enabled a POSA to predict whether those other forms existed, and in fact there was no way for a POSA to predict what polymorph might be obtained before starting actual testing. DFF ¶ 51. Of course, Dr. Trout was compelled to agree with the opinion he offered in the first litigation: that "[t]he range and combinations of crystal growth structures are virtually infinite

and there is no way to guarantee the preparation of additional polymorphs of a substance, much less the generation of all of them." Tr. 922:12–17 (Trout); DFF ¶ 64. As in *Entresto*, a POSA with the Malate Salt Patents in hand would not have known of or foreseen crystalline cabozantinib (L)-malate salts other than Forms N-1 and N-2. 2023 WL 4405464 at *15.

The *Entresto* plaintiff argued that the specification nevertheless satisfied written description, because it disclosed "structural features" of the claimed genus: specifically, the common chemical name and formula. *Id.* at *22. That argument failed because written description "requires that common structural features be described with enough precision that a relevant artisan can visualize or recognize the members of the genus." *Id.* Here, Dr. Trout advanced the same arguments, relying on the common chemical structure, name, and formula for each form of crystalline cabozantinib (L)-malate. *See* PDX 6.18; Tr. 866:11–21 (Trout). But the features of Forms N-1 and N-2 do not reflect those of other crystalline forms. Instead, what Exelixis has done is describe two closely related species that are *not* closely related in structure to other forms—in other words, "merely drawing a fence around the outer limits of a purported genus," which "is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and … not just a species." *Ariad*, 598 F.3d at 1350.

Like the *Entresto* plaintiff, Exelixis also cannot identify "physical properties, or other properties" described in the specification that are representative of the claimed genus. 2023 WL 4405464 at *21; DFF ¶ 54. While the specification reports the "improved properties" of Forms N-1 and N-2, DFF ¶ 55, Drs. Shah and Trout both agreed with Dr. Steed that different crystalline polymorphs can have different properties. DFF ¶ 26. And these are not hypothetical differences. The evidence showed that different known crystalline forms of cabozantinib (L)-malate have different melting points, hygroscopicity, solvation states, and solubilities. DFF ¶¶ 56–62; *see*

Amgen, 872 F.3d at1374 ("the use of post-priority-date evidence to show that a patent does not disclose a representative number of species of a claimed genus is proper"). And Dr. Trout agreed that significant differences in these characteristics can affect the manufacturability, performance, and quality of a drug product. DFF ¶ 63. Indeed, prior-art cautionary tales like Norvir show that one crystalline form of an API may work very differently from another. DFF ¶ 30.

This court's recent decision in *Allergan USA, Inc. v. MSN Laboratories Private Ltd.*, 2023 WL 6295496 (D. Del. Sept. 27, 2023), is also instructive. In that case, the eluxadoline compound was known in the art, and the claims were directed to oral formulations of the compound. Despite broad claims, the specification "only disclose[d] a relatively narrow group of eluxadoline formulations" and thus did not provide written-description support for the full scope of the claims. *Id.* at *6. Here, a narrow species—only two closely related crystalline forms—has been disclosed. That is not enough to disclose to a POSA that any crystalline form of cabozantinib (L)-malate will have the same or similar structural features or physical properties as those forms.

Exelixis has drawn an expansive fence around a genus by claiming all forms of crystalline cabozantinib (L)-malate salt, with nothing more than "a research plan, leaving it to others [including MSN] to explore the unknown contours of the claimed genus." *Entresto*, 2023 WL 6295496 at *22 (quoting *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014)). The claims are invalid for lack of adequate written description.

IV. OBVIOUSNESS-TYPE DOUBLE PATENTING OF THE MALATE SALT PATENTS

More than a decade before the Malate Salt Patents issued, Exelixis was granted the '473 patent, which covers the cabozantinib compound and "pharmaceutically acceptable salts thereof." DFF ¶¶ 65–66. That patent was found valid at the last trial between Exelixis and MSN, giving Cabometyx patent protection through at least 2026. *See Exelixis, Inc. v. MSN Lab'ys Pvt. Ltd.*,

2023 WL 315614 (D. Del. Jan. 19, 2023); DFF ¶ 65. Exelixis should not be permitted via the Malate Salt Patents to extend its patent exclusivity on pharmaceutically acceptable salts of cabozantinib. "Prohibiting double patenting prevents a patentee from obtaining sequential patents on the same invention and obvious variants, to thereby effectively manufacture a timewise extension of its patent exclusivity through a later-expiring patent." *Novartis Pharms. Corp. v. Breckenridge Pharm. Inc.*, 909 F.3d 1355, 1362 (Fed. Cir. 2018). Because there are no patentably distinct differences between claim 5 of the '473 patent and the asserted claims of the Malate Salt Patents, they should be found invalid.

A. There are no patentably distinct differences between claim 5 of the '473 patent and claim 4 of the '439 patent.

1. Pharmaceutically acceptable salts of cabozantinib include crystalline cabozantinib (l)-malate.

Claim 4 of the '439 patent covers crystalline cabozantinib (L)-malate salt with no additional limitations. DFF ¶ 2. The parties do not dispute that crystalline (L)-malate is a pharmaceutically acceptable salt of cabozantinib. DFF ¶ 67. Thus, claim 5 of the '473 patent literally encompasses claim 4 of the '439 patent. Put another way, the species of crystalline cabozantinib (L)-malate is encompassed by the genus of pharmaceutically acceptable salts of cabozantinib. DFF ¶ 68. Claim 4 of the '439 patent, therefore, is not patentably distinct.

The Federal Circuit decisions in *Eli Lilly & Co v. Barr Laboratories* are instructive. 222 F.3d 973 (Fed. Cir. 2000), on reh'g, 251 F.3d 955 (Fed. Cir. 2001) (affirmed in relevant part). In that case, the asserted claim covered the administration of a salt—fluoxetine hydrochloride. 222 F.3d at 976. Applying the double-patenting analysis, the panel concluded that fluoxetine hydrocholoride was one of the compounds "encompassed by" a reference patent claim that covered "acid addition salts" of the "same class of compounds" that included fluoxetine. *Id.* at 980, 986. It found the claim invalid where "the same party *claims* a genus in an earlier patent and then *claims*

a species in a later patent." *Id.* at 986. In so doing, the panel observed that "double patenting is not concerned with what one skilled in the art would be aware [of] from reading the claims but with what inventions the claims define." *Id.*

On rehearing, the Federal Circuit affirmed the finding of obviousness-type double patenting based on a different reference; there, one directed to a method for treating anxiety in a human by administering an effective amount of fluoxetine or a pharmaceutically acceptable salt thereof. 251 F.3d at 969–70. The Court held that "a person of ordinary skill in the art would have recognized that fluoxetine hydrochloride is a pharmaceutically acceptable salt of fluoxetine," noting that hydrochloride salts are obvious compounds based on their common usage. *Id.* at 969. Likewise, here, while not as commonly used as hydrocholoride salts, there is no dispute that malate salts had been used and were known in the prior art as pharmaceutically acceptable. DFF ¶ 71.

Exelixis should not be permitted to use the "broad coverage" of claim 5 of the '473 patent "as both a sword and a shield." *Eli Lilly*, 222 F.3d at 986. Applied here, "[a]s a corollary to [Exelixis]'s expansive right of exclusivity, the ['473 patent] specification satisfied the written description requirement … and the enablement requirement by providing a specification that taught one of ordinary skill in the art how to make and use [a salt of cabozantinib (L)-malate]." *Id.* at 986–87. As this Court recognized, "the malate salt claims could be thought of as … dependent claims from the reference patent." Tr. 1090:22–25. Yet Exelixis already prevailed on the earlier-expiring '473 patent directed to pharmaceutically acceptable salts of cabozantinib. Exelixis should not be able to "hide behind its once-advantageous broad coverage … and argue that selecting [cabozantinib (L)-malate] from the class of compounds defined by [the '473 patent] would not have been obvious." *Eli Lilly*, 222 F.3d at 986.

2. A POSA would have been motivated to prepare crystalline cabozantinib (L)-malate with a reasonable expectation of success.

Even if the Court were to find there is a difference between the pharmaceutically acceptable salts of cabozantinib in claim 5 of the ’473 patent and crystalline cabozantinib (L)-malate salt, that difference is not patentably distinct, because it would have been obvious for a POSA to prepare the crystalline malate salt with a reasonable expectation of success.

To begin, there should be no dispute that a POSA would have been motivated to prepare a salt of cabozantinib. It is specifically claimed by the ’473 patent. DFF ¶ 66. Half of all drug products have API in salt form. DFF ¶ 8. And the prior art taught the advantages of using salts to improve properties of an API for use as drugs. Tr. 432:2–24 (Steed); DTX-177.1; DFF ¶ 25.

There should also be no dispute that identifying a suitable salt form of a drug would have been a matter of routine experimentation well within the skill of a POSA. By 2009, salt screening was a known method used to identify potential salt forms of a drug substance, often outsourced to a contract resource organization and completed within a matter of weeks. DFF ¶ 9. And Exelixis concedes that there is nothing about the cabozantinib molecule that would have made the salt screen experiments particularly complex. DFF ¶ 70.

The trial evidence established the routine and customary path a POSA would have followed to prepare the crystalline (L)-malate salt of cabozantinib during a salt screen. A POSA would begin by straightforward testing of the free base’s solubility and pK_a, which is an inherent measurement of a compound’s propensity to form a salt. DFF ¶¶ 10–11, 14. A POSA would then select 15–20 potential counterions to test and assess compatibility with the free base. DFF ¶ 12. To make those selections, a POSA would look to the prior art identifying FDA-approved pharmaceutically acceptable acid counterions. DFF ¶¶ 13, 71; *see also Pfizer*, 480 F.3d at 1366 (“[I]n selecting an acid addition salt formulation, one skilled in the art looked to pharmacopoeias and compendia to

find a salt that was previously approved by the FDA and used successfully within the pharmaceutical industry."). At the priority date, the literature consistently identified a universe of about 50 potential acids, including malic acid. DFF ¶ 13.

A POSA would also rely on prior art guidance and the published pK_a of known acids to narrow the pool of potential counterions. DFF ¶ 76. Tong's "Rule of 2" would be applied by a POSA to identify potential acids having a pK_a at least two units lower than cabozantinib, because those would be the most likely to form a salt. *Id.* Dr. Trout conceded that this was a "well-known rule of thumb" that a POSA would have known and considered when selecting counterions for a salt screen. DFF ¶ 15. Indeed, the Pharmorphix report notes that malic acid was included in the salt screen during the development of Exelixis' product based on Tong's Rule of 2. DFF ¶ 78.

A POSA would further prioritize the selection of counterions that were known to be safe and non-toxic. DFF ¶ 73. (L)-malic acid, sometimes referred to as apple acid, was known to be one such option. *Id.* For example, Bighley identified (L)-malic acid as one of twelve organic acids that "rarely exhibit toxicity" and can be used to avoid issues that can be encountered with mineral acid salts. DFF ¶ 74. The prior art also taught that "some substances may be considered unobjectionable because they are used profusely in food processing" and are designated as "Generally Recognized as Safe" (GRAS) by FDA. DFF ¶ 82. A POSA would consider GRAS status to be desirable when selecting a counterion for a salt screen, and (L)-malic acid had been designated as GRAS. DFF ¶ 83.

Considering these criteria, as a POSA would have done, there are a relatively limited set of previously used pharmaceutically acceptable counterions that meet Tong's Rule of 2 for cabozantinib and were recognized as safe. DFF ¶ 84. Dr. Steed testified that list would have been easily encompassed by a routine salt screen of 15–20 counterions. DFF ¶ 84. For example, a POSA

would have considered the Stahl reference, which provided "a revised list of useful salt-forming acids and bases" based on "[a]ccumulated knowledge and experience" of "acids and bases regarded as innocuous" since earlier lists provided by Berge and Bighley. DFF ¶ 81. At trial, it was established that only nine acids identified by Stahl were designated GRAS and met Tong's Rule of 2 for cabozantinib. DFF ¶ 84. Malic acid was one of them. *Id.*[3] As Dr. Steed explained, it would have been obvious at the priority date to include the limited number of acids that met these criteria in a salt screen for cabozantinib. *Id.*

Exelixis' primary rebuttal to the obvious selection of malic acid is the relatively infrequent use of malate salts in previous FDA-approved drugs. But that ignores that one of the few FDA-approved TKIs was a malate salt and would not dissuade a POSA from selecting malic acid for a cabozantinib salt screen. DFF ¶ 72. Indeed, the Federal Circuit in *Pfizer* recognized that "beyond hydrochloride, which was used in approximately 43% of approved drugs, almost all other salts could be characterized as 'rarely used.'" *Pfizer*, 480 F.3d at 1363. In that case, the Federal Circuit reversed the District Court's judgment that the besylate salt of amlodipine was non-obvious. *Id.* at 1372. The Court found: "That benzene sulphonate was only used in creating 0.25% of FDA-approved drugs is not highly probative, much less dispositive." *Id.* at 1363. Rather, the *Pfizer* Court recognized a POSA would have "favorably considered" benzene sulphonate out of Berge's list of 53 anions based on the teachings of the prior art. *Id.* Likewise, here, a POSA guided by the prior art would have favorably considered malic acid for the cabozantinib salt screen based on the narrowing criteria discussed above.

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[3] Dr. Steed also explained that a POSA would have been further motivated to include malic acid in a salt screen: (1) based on its structural compatibility with cabozantinib, which would have led a POSA to expect them to be likely to form a stable crystal; and (2) because another FDA-approved tyrosine kinase inhibitor, sunitinib, had been formulated as an (L)-malate salt, which would have indicated to a POSA that (L)-malic acid is a suitable acid for those types of drugs. DFF ¶¶ 72, 85.

Finally, a POSA would have been motivated to prepare a crystalline form of cabozantinib (L)-malate during the salt screen due to the desirable properties of crystalline salts. DFF ¶ 88. Over 90% of drugs are crystalline, and the prior art reflects a strong preference for use of crystalline over amorphous forms of drugs. DFF ¶ 21. Indeed, Gibson teaches that "[a]ttempts to crystallize [an] amorphous [solid] should always be undertaken" because of problems associated with the physical and chemical stability of amorphous forms. DFF ¶ 22. And there is no dispute that a POSA would be well aware of methods to prepare crystalline forms of salts. DFF ¶ 28.

While the results of a salt screen are not guaranteed—that is the reason for doing the screen—a POSA would have had a reasonable expectation of success of being able to prepare a crystalline cabozantinib (L)-malate salt. The Federal Circuit has observed that while there is "some degree of unpredictability in salt formation … the mere possibility that some salts may not form does not demand a conclusion that those that do are necessarily non-obvious." *Pfizer*, 480 F.3d at 1366. "Indeed, a rule of law equating unpredictability to patentability … would mean that any new salt … would be separately patentable, simply because the formation and properties of each salt must be verified through testing." *Id.* at 1364. The Court held "[t]his cannot be the proper standard since the expectation of success need only be reasonable, not absolute." *Id.* Here, a POSA would have reasonably expected an (L)-malate salt of cabozantinib to form, based on Tong's Rule of 2. DFF ¶ 15. And a POSA would have known that most salts formed in a screen are able to be crystallized under a range of experimental conditions. DFF ¶ 16.

Thus, following the routine and customary path of a salt screen, it would have been obvious for a POSA to prepare crystalline cabozantinib (L)-malate, analyze its properties, and determine it

was suitable for further pharmaceutical development. DFF ¶ 86.[4]

B. There are no patentably distinct differences between claim 5 of the ’473 patent and claim 3 of the ’440 patent or claim 2 of the ’015 patent.

The additional claim limitations of the ’440 and ’015 patents are not patentably distinct over claim 5 of the ’473 patent, because they too would have been obvious to a POSA.

Claim 3 of the ’440 patent includes the added limitation that the crystalline cabozantinib (L)-malate be in “a pharmaceutical composition.” DFF ¶ 3. But including a pharmaceutically acceptable salt in a pharmaceutical formulation is beyond obvious. Lest there be any doubt, a POSA determining whether crystalline cabozantinib (L)-malate salt could be used in a pharmaceutical composition would need look no further than the prior art application that led to the ’473 patent, U.S. Pat. Pub. No. 2007/0054928 (“the ’928 application”). The ’928 application teaches administration of compounds that include cabozantinib or their pharmaceutically acceptable salts “in pure form or in an appropriate pharmaceutical composition.” DTX-180.145; DFF ¶ 90. Thus, a POSA would have been motivated to prepare and found obvious a pharmaceutical composition of crystalline cabozantinib (L)-malate. DFF ¶ 92.

Claim 2 of the ’015 patent includes the additional limitation of administering crystalline cabozantinib (L)-malate as “a method of treating cancer … wherein said cancer is kidney cancer.” DFF ¶ 4. Again, the ’928 application explicitly discloses this limitation. It teaches that compositions of the invention, including cabozantinib and its pharmaceutically acceptable salts, “are used to treat diseases associated with abnormal and or unregulated cellular activity. Disease states which can be treated by the methods and compositions provided herein include, but are not

[4] This is readily confirmed by the testimony of Peter Lamb, Exelixis’s Executive Vice President of Scientific Strategy, who evaluated Pharmorphix’s cabozantinib salt screen report and selected the (L)-malate salt as the one with the most desirable properties within 30–60 minutes of receiving the results. DFF ¶ 88.

limited to, cancer …" DTX-180.04–05; DFF ¶ 93. And the '928 application defines cancer to include kidney cancer. DTX-180.143; DFF ¶ 93. Thus, a POSA would have been motivated to use and found obvious administration of crystalline cabozantinib (L)-malate as a method for treating kidney cancer. DFF ¶ 95. At trial, this testimony went essentially unrebutted by Exelixis.

For the above reasons, none of the asserted claims of the Malate Salt Patents are "patentably distinct" from claim 5 of the '473 patent. Exelixis should not be permitted to manufacture a timewise extension of patent exclusivity through the later-expiring Malate Salt Patents. The Court should invalidate those patents based on obviousness-type double patenting.

V. OBVIOUSNESS OF CLAIM 3 OF THE '349 PATENT

Claim 3 of the '349 patent generally requires an oral capsule or tablet formulation of cabozantinib (L)-malate and certain excipients that is "essentially free" of the 1-1 impurity, meaning less than 200 ppm of the 1-1 impurity. DFF ¶ 5. Here, cabozantinib (L)-malate API and its uses, including in oral formulations, were already known. A "strong market [pressure]" also existed to formulate a composition with low levels of the claimed impurity—the FDA required that GTIs like the 1-1 impurity be present at low levels. *Purdue Pharma L.P. v. Accord Healthcare Inc.*, No. 20-cv-1362-RGA, 2023 WL 2894939, at *19 (D. Del. Apr. 11, 2023) ("FDA communications can introduce a market force incentivizing a particular invention").

Formulating the claimed compositions would have been routine. DFF ¶¶ 183–196. The inventor, Dr. Shah, and the parties' experts, Drs. Myerson and Donovan, explained that the "key" is starting with API that is essentially free of the 1-1 impurity, which ensures that the formulated capsules and tablets will also be essentially free of the 1-1 impurity. DFF ¶ 193.

To obtain cabozantinib (L)-malate API essentially free of the 1-1 impurity, a POSA would have only had "a finite number of identified, predictable solutions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007). One would have been to simply use the prior art API manufacturing

process—Brown Example 1 *inherently* produces cabozantinib (L)-malate with low levels of the 1-1 impurity. Even if the Court finds that this process does not inherently produce the desired API, another predictable solution existed: purify the cabozantinib (L)-malate API with a conventional recrystallization technique. Indeed, the "removal [of the 1-1] is [] the result of applying routine [recrystallization] techniques to what a highly skilled POSA would have seen as a simple problem." *Purdue*, 2023 WL 2894939 at *24. Not only was recrystallization a "conventional" and "highly effective method" of purifying an API, the FDA recommended using recrystallization to purge GTIs like the 1-1 impurity. DFF ¶¶ 113, 178. Claim 3 of the '349 patent is invalid as obvious.

A. Brown Example 1 inherently produces cabozantinib (L)-malate essentially free of the 1-1 impurity.

Clear and convincing evidence—in the form of expert testimony and undisputed testing data—shows that cabozantinib (L)-malate essentially free of the 1-1 impurity is "the natural result" of the Brown Example 1 process. *Hospira*, 946 F.3d at 1329. The trial evidence included "not only … several examples of [batches] that exhibit the [essentially free] limitation[]," but also "expert testimony confirming the scientific principles underlying that result." *Par Pharm., Inc. v. TWi Pharms., Inc.*, 120 F. Supp. 3d 468, 475 (D. Md. 2015), *aff'd*, 624 F. App'x 756 (Fed. Cir. 2015); *see also Hospira*, 946 F.3d at 1328, 1330 (affirming finding of inherency based on testing data and scientific expert testimony); DFF ¶¶ 136–162.

As detailed below, the parties' experts agreed on the scientific principles explaining why Brown Example 1 results in API essentially free of the 1-1 impurity. In addition, undisputed data confirms that every batch manufactured according to Brown Example 1 produced API with less than 50 ppm of the 1-1 impurity. DFF ¶¶ 160–161. Exelixis provided no persuasive evidence to the contrary; only flawed speculation in response to MSN's showing of inherency.

1. Expert testimony confirms that Brown Example 1 inherently produces cabozantinib (L)-malate essentially free of the 1-1 impurity.

At trial, MSN's expert, Dr. Lepore, testified that the Brown Example 1 process necessarily and inherently results in cabozantinib (L)-malate API that is essentially free of the 1-1 impurity. DFF ¶ 135. Exelixis' expert, Dr. MacMillan, did not provide an ultimate opinion on the inherency issue, but he did agree with all the scientific principles explaining why the 1-1 impurity would not be present in API from Brown Example 1. DFF ¶¶ 139–154. Exelixis' other expert, Dr. Myerson, disputed that Brown Example 1 inherently results in the desired API based on an errant batch manufactured by Girindus, but he too agreed with the underlying scientific principles. *Id*.

There is no dispute among the experts how the 1-1 impurity could arise—three routes exist: (1) as a starting material that carries through to the final API, (2) as a degradation product, or (3) as a byproduct. DFF ¶ 139. And it is undisputed that none of these routes would lead to levels of the 1-1 impurity above 200 ppm in the API from Brown Example 1. DFF ¶¶ 140–154.

While the 1-1 impurity is the starting material used in Brown Example 1, the undisputed trial evidence was that residual 1-1 would be purged by the end of the process. DFF ¶¶ 141–147. Brown Example 1 has five steps. DFF ¶ 142. In the first step, nearly all the 1-1 starting material is consumed in a reaction. DFF ¶ 143. Each of the five steps also has its own purification process. DFF ¶ 142. Drs. Lepore and MacMillan explained that step one's purification included an effective method referred to as "crystallization," which would leave only a "very small amount" of the 1-1 impurity. DFF ¶ 144; *see also* DFF ¶ 182. Any remaining 1-1 impurity, Dr. MacMillan explained, would be purged in the four subsequent purifications. DFF ¶ 145. And in addition to the purifications, Dr. MacMillan testified that other reagents in the Brown Example 1 process would also purge the 1-1 impurity. DFF ¶ 146. Thus, the 1-1 starting material would be purged during the Brown Example 1 manufacture of cabozantinib (L)-malate API. DFF ¶ 147.

The trial evidence was undisputed that Brown Example 1 does not form the 1-1 impurity as a degradation product. DFF ¶ 148. Dr. MacMillan testified that degradation of the molecule to form the 1-1 impurity would not occur because the molecule's bond that would need to degrade is "very stable." DFF ¶ 149. After analyzing the molecule's chemical structure and its functional groups, Dr. MacMillan provided further reasons why degradation would not occur, including because hydrolysis would not occur, the salt formation of cabozantinib would make the compound even more stable, and the reagents used in the process would not catalyze the formation of the 1-1 impurity. DFF ¶¶ 150–152. Like in *Hospira*, "the evidence [and] expert testimony that … [cabozantinib (L)-malate] is a very stable drug" supports a finding of inherency. 946 F.3d at 1330.

There is also no evidence that the 1-1 impurity forms as a byproduct. Brown Example 1's synthetic scheme confirms that 1-1 is not a byproduct. DFF ¶ 153. Even if it was, the experts agreed the purifications between each step would purge it, and Dr. MacMillan testified that "a POSA would not have expected the 1-1 impurity to have formed as a result of the Brown process." *Id*. Because "[t]estimony from [Exelixis'] own expert[s] explained [the scientific principles]" underlying why the Brown Example 1 produces API essentially free of the 1-1 impurity, the only conclusion is that the limitation is inherent. *3form, Inc. v. Lumicor, Inc.*, 678 F. App'x 1002, 1009 (Fed. Cir. 2017) (affirming summary judgment of inherency).

2. The relevant data confirms that Brown Example 1 inherently produces cabozantinib (L)-malate essentially free of the 1-1 impurity.

Undisputed data confirms the experts' testimony on the scientific principles—every batch manufactured by Brown Example 1 produced API with less than 50 ppm of the 1-1 impurity. Regis manufactured three batches of cabozantinib (L)-malate according to the Brown Example 1 process. DFF ¶ 155. At trial, Dr. Lepore presented the "step-by-step" detailed synthetic scheme and narrative description of the Brown Example 1 process. DFF ¶¶ 119, 156–157. He then compared

each step side-by-side with the detailed description of the Regis manufacturing process. *Id*. After comparing each step of both processes, Dr. Lepore concluded that the two were the same. *Id*. Dr. Myerson conceded that the Brown Example 1 process and the Regis process were identical. *Id*. Testing of the Regis Batches conclusively showed that Brown Example 1 produces cabozantinib (L)-malate with fewer than 50 ppm of the 1-1 impurity—far below the 200 ppm limit required by the claim. DFF ¶¶ 160–161. This undisputed data thereby confirms that Brown Example 1 inherently produces API essentially free of the 1-1 impurity. DFF ¶ 135.

3. Exelixis presented no persuasive evidence to undermine the showing of inherency.

Dr. Myerson conceded that the Regis Batches (made according to Brown Example 1) produced API with less than 200 ppm of the 1-1 impurity. DFF ¶ 160. But he disputed that the process would necessarily do so, based primarily on an errant and irrelevant batch manufactured by Girindus. Tr. 719:4–16. Dr. Myerson opined that the Girindus batch was also "made according to … the Brown process." Tr. 714:18–715:4. Thus, in his view, because the Girindus Batch had higher levels of the 1-1 impurity, Brown Example 1 does not necessarily result in API essentially free of the 1-1 impurity. Tr. 815:17–816:10. But Dr. Myerson essentially ignored that Girindus failed to follow Brown Example 1. In fact, the Girindus process had more than six "planned deviations" where it altered the process. DFF ¶ 164. Dr. Myerson's claim that "those planned deviations still fall [] within the scope of Brown," Tr. 716:18–717:2 (Myerson) is wrong.

As a matter of law, the Girindus Batch is irrelevant to the inherency inquiry because "an experiment that d[oes] not follow the [prior art process] is not probative of what would inevitably occur if the [prior art process] were followed." *Merck & Cie v. Watson Lab'ys, Inc.*, 125 F. Supp. 3d 503, 513 (D. Del. 2015), *rev'd on other grounds*, 822 F.3d 1347 (Fed. Cir. 2016).

As a matter of fact, the Girindus Batch omitted a critical purification step, which would

have purified the 1-1 impurity, and included fundamental changes to the chemistry. DFF ¶¶ 166–168. Dr. Lepore explained that Girindus failed to perform step one's crystallization purification—the same step that Dr. MacMillan agreed would have purged the 1-1 impurity. DFF ¶¶ 144, 166. In another deviation, Girindus added an entirely new step not found in Brown Example 1 that produced a new intermediate. DFF ¶ 167. Dr. MacMillan explained that "a different number of steps," such as this additional step that Girindus inserted, "means [that] different chemistries [are] involved." Tr. 674:16–25. In other deviations, Girindus exposed the compound to heat, water, and acid, and left the material exposed to those conditions standing over a weekend—conditions that Dr. Lepore's unrebutted testimony explained are not in the Brown Example 1 process. DFF ¶ 168.

Dr. Myerson's speculation that the Girindus deviations were made to increase yield and overall purity does nothing to change the fact that Girindus skipped a purification step and fundamentally altered the chemistry. Tr. 717:6–16; DFF ¶¶ 164–168. Moreover, Dr. Myerson's justification that "the deviations were done in steps that would not be expected to produce the 1-1 impurity" turns out to be a straw man—Dr. Myerson had already testified that *none* of the steps of Brown Example 1 were expected to produce the 1-1 impurity. Tr. 717:20–21; 709:3–19.

Realizing that the Girindus batch does not undermine MSN's clear showing of inherency, Dr. Myerson attempted to pivot, and, for the first time at trial, presented two new opinions.[5] First, Dr. Myerson claimed that the use of the term "approximately" in Brown Example 1 means that the process is variable. Tr. 783:21–784:7. He never actually drew the connection, but his implication

[5] Dr. Myerson admitted he never previously disclosed these two opinions, and, therefore, the testimony should be stricken or disregarded. Tr. 784:11–16 ("I didn't express an opinion about approximately in the example, that's true."); Tr. 788:22–25 (Q: "[Y]ou testified at your deposition differently than you're testifying today?" A: "Right."); *Allergan USA, Inc. v. MSN Lab'ys Pvt. Ltd. et al.*, No. CV 19-1727-RGA, D.I. 480, at 3 (D. Del. Aug. 4, 2023) (striking expert testimony presented "for the first time at trial.").

was that the variability from the word "approximately" could lead to variable levels of the 1-1 impurity above 200 ppm. Second, Dr. Myerson claimed that Dr. Lepore conceded on cross-examination that a vague statement in Exelixis' IND that some "changes were implemented for the GMP batch" manufactured by Regis meant that Regis deviated from the Brown Example 1 process. Tr. 788:4–25. But Dr. Lepore made no such concession—he testified that the statement in the IND likely referred to "extremely minor things" that neither Dr. Lepore, Exelixis, or Regis characterized as deviations, and the details of which Exelixis did not produce. Tr. 338:2–24.

Dr. Myerson's new opinions are inconsistent with his direct testimony. In one breath, Dr. Myerson speculates that the use of the term "approximately" in Brown Example 1 could result in variable levels of the 1-1 impurity. Tr. 784:2–10. But in another breath, he touts that the '349 patent process "consistently" results in low levels of the 1-1 impurity, despite that it also uses the term "approximately." Tr. 783:21–784:7. Similarly, Dr. Myerson speculated that purported "changes" in the Regis process were material changes whereas Girindus's expressly identified "deviations" were somehow within the scope of Brown. Tr. 716:1–4.

But Dr. Myerson's clashing opinions can be set aside because they all miss the point. Like all synthetic processes, Brown Example 1 *allows* for variability. DFF ¶¶ 138, 159. In fact, the term "approximately" is regularly used in synthetic chemistry, including in both Brown Example 1 and the '349 patent, to describe parameters that "do not have to be precise." DFF ¶ 158. Indeed, Dr. Lepore explained that although "100% exact reproducibility is not attainable in any scientific experiment" because there is "always variability in a synthetic process," persons of ordinary skill are still able to faithfully follow the process. DFF ¶ 135; Tr. 333:14–18 (Lepore); 787:5–7 (Myerson). Dr. Shah testified that a variable process like the '349 patent can nevertheless be "a consistent reproducible manufacturing process" to synthesize cabozantinib (L)-malate that is

essentially free of the 1-1 impurity. DFF ¶ 138. The same is true of Brown Example 1, which, when faithfully followed, produces API essentially free of the 1-1 impurity. DFF ¶ 135. Dr. Myerson's newfound opinions are nothing more than speculation. The undisputed evidence at trial was that Regis "follow[ed] Brown within the variability of Brown," and produced API essentially free of the 1-1 impurity. DFF ¶¶ 159–160.

Dr. Myerson's speculation is much like in *Par*, where the court found, "while [the patentee] implies that other counterexample formulations might exist, it does not actually come forward with any," and therefore "has failed to rebut [the] inherency case." *Par Pharm.*, 120 F. Supp. 3d at 475. It is also the type that the Federal Circuit has deemed insufficient to avoid inherency, because Exelixis "did not present evidence of even a single [batch] of the [API manufactured by Brown Example 1] that failed to meet the [essentially free of 1-1] limitation." *Hospira*, 946 F.3d at 1330. "All of the evidence on record therefore shows that [Brown Example 1] results in [cabozantinib (L)-malate] having [low ppm levels of the 1-1 impurity]." *3form*, 678 F. App'x at 1010.

B. It would have been obvious to a POSA to produce cabozantinib (L)-malate essentially free of the 1-1 impurity.

Even if the Court finds that Brown Example 1 does not *inherently* produce cabozantinib (L)-malate API with less than 200 ppm of the 1-1 impurity, it would have nonetheless been obvious to produce cabozantinib (L)-malate API that was essentially free of the 1-1 impurity. As of the priority date, FDA Guidance taught that GTIs, like the 1-1 impurity, should be controlled to low ppm levels. DFF ¶¶ 170–176. As such, a POSA would have been highly motivated to "meet [that] particular threshold … since failure to meet that requirement would exclude the product from the market." *Purdue*, 2023 WL 2894939, at *19. FDA Guidance also provided an obvious solution if the drug did not meet the required purity threshold—add a purification step to remove the relevant impurity. DFF ¶¶ 177–182. Specifically, FDA recommended the use of recrystallization, a

conventional, highly effective method to purify API. DFF ¶¶ 113, 178. Thus, "removal in the invention itself is [] the result of applying routine techniques to what a highly skilled POSA would have seen as a simple problem." *Purdue*, 2023 WL 2894939 at *24.

There is no dispute that a POSA would have identified the 1-1 impurity as a GTI, that the FDA required it be controlled at low ppm levels, and that recrystallization was a conventional purification technique. DFF ¶¶ 170–182. The only issue Exelixis seriously contests is whether a POSA would have had a reasonable expectation of success that recrystallization would have worked to purify the API to less than 200 ppm of the 1-1 impurity. The evidence at trial showed that the POSA would have reasonably expected success using routine recrystallization.

1. FDA Guidance would have led to identification of the 1-1 GTI impurity.

While the prior art did not expressly disclose that the 1-1 impurity was a GTI, there is no dispute a POSA would have identified it by following FDA Guidance. DFF ¶ 175. Dr. Lepore explained that the 1-1 impurity is the starting material for manufacturing cabozantinib, residual starting materials were a known source of GTIs, and FDA Guidance on screening for potential GTIs "applie[d] to known starting materials." DFF ¶ 108. FDA Guidance, therefore, would have motivated a POSA to assess the 1-1 starting material for genotoxicity. DFF ¶¶ 170–175.

The prior art taught a well-known approach for assessing whether a starting material is genotoxic. First, the impurity is evaluated for "whether there is a structural alert." DFF ¶ 104. If so, then the impurity is screened in an Ames test to determine whether it is a GTI. DFF ¶ 105. Drs. Lepore and Myerson agreed that a POSA would have been able to simply look at the known chemical structure of the 1-1 starting material, see that it is of the quinoline class of compounds, and know that meant there was a structural alert because many quinolines were known to be genotoxic. DFF ¶ 111–112. Because of the structural alert, a POSA would have screened the 1-1 impurity via the Ames test and determined it was a GTI. DFF ¶¶ 174–175; *Purdue*, 2023 WL

2894939, at *19–20 (“suspicion that ABUKs were toxic existed even before [the FDA low-ABUK requirements]” because “ABUKs were long known to be genotoxic.”).

2. FDA Guidance would have required the control of the 1-1 impurity to low ppm levels.

Because the 1-1 starting material is a GTI, a POSA would have known that the FDA Guidance required it be controlled to low ppm levels. DFF ¶¶ 106–107. Dr. Lepore provided uncontroverted testimony explaining that to use a drug in clinical trials, the FDA provided acceptable daily intake levels for GTIs, and that under these circumstances, a POSA would have known that the presence of the 1-1 impurity in cabozantinib (L)-malate API would have been required to be at levels below 50 ppm. DFF ¶ 176.

Dr. MacMillan testified that a POSA would not have been motivated to control for the 1-1 impurity, because there would have been no 1-1 impurity present in the API at the end of the Brown Example 1 process. Tr. 668:16–669:6. While Dr. MacMillan’s justification for not controlling the impurity is correct—Brown Example 1 inherently produces API that is essentially free of the 1-1 impurity—he conceded that he neglected to consider any FDA Guidance on starting-material impurities. Tr. 681:21–682:8. Dr. Lepore explained that FDA Guidance is unequivocal—it “applies to known starting materials,” such as the 1-1 impurity, regardless of whether the starting material is purged during the process. DFF ¶ 108. Dr. MacMillan’s flawed testimony is also undermined by Dr. Myerson, who admitted a POSA would have understood that because the 1-1 impurity was a GTI it therefore needed to be “minimize[d].” Tr. 771:17–772:3; DFF ¶ 17.

3. FDA Guidance recommended the use of recrystallization as a GTI control strategy.

A POSA would have had a clear motivation to minimize the 1-1 impurity down to the low ppm levels required by the ’349 patent. “[A] POSA seeking to reduce [1-1] levels would have a finite, small, and easily identified set of options,” because the same FDA Guidance that required

low limits for GTIs also provided a solution—change the purification route. *Purdue*, 2023 WL 2894939, at *21; DFF ¶¶ 177–178. It would have been readily apparent to a POSA that the 1-1 impurity could be removed using recrystallization. Dr. Lepore testified that it would have been the "first thing" a POSA would have attempted; Dr. Wilson conceded that recrystallization was a known method to reduce the presence of GTIs; and Dr. Myerson admitted that a POSA would have been interested in using recrystallization to remove GTIs. DFF ¶¶ 177, 114, 180. Moreover, Dr. Myerson volunteered that recrystallization is "usually the final purification step in the manufacture of any API." Tr. 793:1–7. Thus "a skilled artisan would have been motivated" to use recrystallization. *Pfizer*, 480 F.3d at 1361.

Despite the clear motivation in the prior art, Exelixis disputes whether there would have been "a reasonable expectation of success in doing so." *Id.* Citing his own textbook on crystallization, Dr. Myerson claims that in some circumstances when the impurity is structurally similar to the API, the impurity may be difficult to remove. Tr. 735:7–736:22. He testified that "a recrystallization step *could* be ineffective in this type of process," (Tr. 738:6–13), and that a POSA "*might* have problems with the specific impurity," (Tr. 794:6–11), because recrystallization "doesn't *always* work," (Tr. 793:19–24), and "won't *necessarily* improve the purity," (Tr. 794:2–5). (emphases added). But Dr. Myerson misapplies the law—"the expectation of success need only be reasonable, not absolute" nor "guaranteed." *Pfizer*, 480 F.3d at 1364.

Aside from the FDA recommending its use, there would have been ample reason for a POSA to expect success. Dr. Wilson testified that recrystallization was a known purification technique used to purge GTIs. DFF ¶ 114. And Dr. Lepore explained that the literature was filled with examples using recrystallization to successfully purify an API, and provided a specific example that purged a GTI down to less than 1 ppm. DFF ¶ 117. "[B]ecause only routine

techniques and commonly possessed training would be required, [a] POSA would have had a reasonable expectation of success" in using recrystallization. *Purdue*, 2023 WL 2894939 at *21.

C. Routine formulation development of cabozantinib (L)-malate would have led to the claimed invention.

With cabozantinib (L)-malate API that was essentially free of the 1-1 impurity in hand, either inherently or via a recrystallization, a POSA would have been motivated to formulate the API into a dosage form for administration. DFF ¶ 183. At trial, the Court questioned whether the compositional limitations of claim 3 of the '349 patent (i.e., a capsule or tablet for oral administration comprising a filler, disintegrant, glidant, and lubricant), were really in dispute between the parties. Tr. 635:3 ("Is this really in dispute?"). The answer is "no"; there is no dispute that these limitations would have been obvious—Dr. Myerson conceded that once you have the cabozantinib (L)-malate API with low ppm levels of the 1-1 impurity, formulating the API to maintain those levels was well within the level of skill in the art. DFF ¶ 196.

In fact, the '349 patent does not disclose "anything additional that would control for the 1-1" impurity aside from a synthetic process for making the API. DFF ¶ 193. The '349 patent only fleetingly describes how to formulate the API into a capsule or tablet, but where it does, the specification instructs that "[t]he compositions are prepared according to methods available to the skilled artisan" and cites to well-known prior art formulation handbooks. DFF ¶ 195. Thus, the '349 patent leaves it "to the person of skill in the art to do those kinds of tasks." DFF ¶ 194.

1. A POSA would have been motivated to formulate cabozantinib (L)-malate into a tablet or capsule comprising a filler, disintegrant, glidant, and lubricant.

The claimed compositional limitations were all disclosed in Brown and well known in the art. Brown disclosed that the "particularly preferred" dosage form for cabozantinib (L)-malate is a capsule or tablet and the dosage form could be formulated by mixing with fillers, disintegrants,

lubricants, and talc, a well-known glidant. DFF ¶ 122. Well-known prior art formulation references, such as Lachman, and references using API analogous to cabozantinib also disclosed the claimed compositional limitations. DFF ¶ 185. For example, Lachman disclosed drug-agnostic prototype formulations that comprise a filler, disintegrant, glidant, and lubricant, and which Dr. Donovan testified "would likely be successful" when used with cabozantinib (L)-malate. DFF ¶ 185. The '081 Application, which related to TKIs like cabozantinib, disclosed that TKIs could be formulated into tablets and capsules comprising fillers, disintegrants, lubricants and glidants. DFF ¶ 186. Dr. Donovan provided unrebutted testimony that these disclosures would have motivated a POSA to formulate a capsule or tablet using the claimed excipients. DFF ¶¶ 184–187.

2. A POSA would have had a reasonable expectation of formulating a tablet or capsule that is essentially free of the 1-1 impurity.

As described above, because a POSA would have identified the 1-1 impurity as a GTI, a POSA would have controlled for it during formulation. Limiting impurities during formulation of a drug product is a fundamental tenet of formulation. DFF ¶ 132. During both preformulation and formulation activities, a POSA would have ensured that no toxic substances were formed. DFF ¶ 131. Further, as required by other FDA guidance, a POSA would have determined whether exposure to any manufacturing conditions could cause formation of the 1-1 impurity. DFF ¶¶ 133–134. Any formation of the 1-1 impurity, however, would have been unlikely, because cabozantinib (L)-malate is a "very stable compound" that is not expected to degrade. DFF ¶ 149. Accordingly, a POSA would have had a reasonable expectation of success that the API could be formulated into a capsule or tablet and remain essentially free of the 1-1 impurity. DFF ¶¶ 188–196.

VI. NO OBJECTIVE INDICIA SUPPORT NON-OBVIOUSNESS.

At trial, Exelixis produced no persuasive evidence of secondary considerations.

A. Exelixis failed to demonstrate nexus.

"[T]he patentee bears the burden of production on nexus" and must "demonstrate[] that any of its proffered evidence relates to the limitations that it has in fact challenged as nonobvious aspects of the claimed invention." *Bombardier Rec. Prods. Inc. v. Arctic Cat Inc.*, 785 F. App'x 858, 870–71 (Fed. Cir. 2019). Here, Exelixis failed to show that any objective indicia relate to purportedly nonobvious aspects as opposed to the known uses and efficacy of cabozantinib.

Highlighting Exelixis' failure, Mr. Tate provided exactly the same analysis of nexus in this case as he did in *Cabozantinib I*, where the obviousness of the cabozantinib API was at issue in the '473 patent. DFF ¶¶ 199–200. Further, Mr. Tate failed to evaluate the patents asserted here against other Orange Book-listed patents, stating that he relied on the "technical experts" to determine whether there is a "link between the technical aspects [of] the claims of the patents" and the objective indicia. Tr. 986:7–21. But Exelixis' technical experts also failed to establish any such link with a purportedly nonobvious claim limitation.

Dr. Myerson testified that "the nexus between the '349 patent and the objective indicia" relates to the '349 patent's disclosure of "a synthetic process to produce cabozantinib (L)-malate." 740:22–7415. But the '349 patent does not claim a synthetic process. DFF ¶ 5. And Dr. George testified that a nexus exists between the clinical benefits of Cabometyx and the '349 patent's requirement that the formulation be essentially free of the 1-1 impurity. Tr. 959:20–960:10. But an equally viable formulation of cabozantinib (L)-malate that is essentially free of the 1-1 impurity could also be formulated without a glidant, which is outside the scope of the asserted claim. DFF ¶ 198. The Federal Circuit has held that when "the claims are broad enough to cover devices that either do or do not solve the [long-felt need], [the] evidence of non-obviousness fails because it is not commensurate in scope with the claims." *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1336 (Fed. Cir. 2010). If anything, Exelixis's evidence of secondary considerations all

stems from the known uses of cabozantinib—precisely what Exelixis argued in *Cabozantinib I*.

B. The existence of a blocking patent discounts any alleged secondary considerations of long-felt, unmet need and commercial success.

Drs. Donovan, Steed, and McDuff offered unrebutted testimony that the ’473 patent and its published parent application blocked entities other than Exelixis from pursuing further development or commercialization of cabozantinib. DFF ¶ 202. Further, Dr. McDuff evaluated the *Acorda* factors, determined that a “strong deterrence” existed, and testified that no inference can be made to support nonobviousness of the Malate Salt Patents or the ’349 patent based on any alleged long-felt but unmet need or commercial success. DFF ¶¶ 202–205. *Acorda Therapeutics, Inc. v. Roxane Lab’ys, Inc.*, 903 F.3d 1310, 1339 (Fed. Cir. 2018) (“[T]he evidence of blocking [] is pertinent [] to the factual question of long-felt but unmet need” and commercial success).

C. Exelixis has not shown the satisfaction of a long-felt, unmet need.

By 2009, there were already eight TKIs that had been approved for cancer treatment and six of those were “spectrum-selective” TKIs that overlap with many of the same targets inhibited by cabozantinib. DFF ¶ 209. For example, Exelixis’s clinician Dr. George admitted that prior to 2009, the FDA had already approved three anti-VEGFR TKIs—sunitinib, sorafenib, and pazopanib—for front-line RCC treatment, and he prescribes those TKIs to the majority of his patients over cabozantinib. DFF ¶ 209; Tr. 965:22–966:4. As such, no long-felt, unmet need for a TKI to treat cancer or kidney cancer existed. *In re Couvaras*, 70 F.4th 1374, 1381 (Fed. Cir. 2023) (“[T]here was no long-felt, unmet need, given the admitted availability of antihypertensive agents.”).

Even if a need existed, cabozantinib did not satisfy it. The existence of a “long-felt need is not sufficient” if “the evidence did not show how the [claimed invention] solved that need.” *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1012 (Fed. Cir. 2018). And here, the

parties' clinicians both agree "there is still an unmet need today to improve RCC treatment on both the front line and subsequent line treatments for RCC." DFF ¶ 216. Further, the parties' clinicians both agreed that cabozantinib has similar toxicity and side effects to the prior art TKIs, and that most RCC patients develop a resistance to cabozantinib just like they do for other TKIs. DFF ¶213. 2013. In fact, the NCCN guidelines for treating RCC patients recommend other preferred regimens aside from cabozantinib, such as immuno-oncology agents. DFF ¶ 211.

D. Exelixis has not shown commercial success.

Commercial success may be relevant "because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Mr. Tate's conclusion that Cabometyx is a commercial success was not supported by any analysis addressing that core question. DFF ¶¶ 217–219. Specifically, Mr. Tate's analysis lacked any "definition of success" to evaluate whether the presented sales and prescriptions were high, low, or somewhere in between; failed to consider development and commercialization costs necessary to bring the product to market to evaluate a return on investment; and provided a "wide range of market shares" with no guidance on whether Cabometyx's market share is high or low. *Id.*

E. Exelixis has not shown that the Malate Salt produced unexpected results.

"[B]y definition, any superior property must be *unexpected* to be considered as evidence of non-obviousness. Thus, in order to properly evaluate whether a superior property was unexpected, the court [must] consider[] what properties were expected." *Pfizer*, 480 F.3d at 1371. Here, Dr. Trout testified in passing that the malate salt of cabozantinib would not have been expected to "feature the best suite of properties." Tr. 886:16–25 (Trout). But neither Dr. Trout nor Dr. Koleng testified that a POSA would have expected the malate salt to have poor properties. To

the contrary, Dr. Trout testified that a POSA would not have any expectation of "what the pharmaceutical properties would be until the salt is made and characterized." Tr. 889:4–6. Dr. Koleng agreed. Tr. 828:3–6. And Dr. Steed confirmed that a POSA's selection of acids for a routine salt screen would not include an expectation that a given acid would not work. DFF ¶ 220.

Exelixis also argues that the dissolution of crystalline cabozantinib (L)-malate was unexpectedly better than the amorphous form, relying primarily on Dr. Shah's declaration to the Patent Office—a declaration that did not characterize the results as unexpected or surprising. DFF ¶ 223. However, as Dr. Steed explained, the solubility of crystalline cabozantinib (L)-malate was not unexpected. Rather, it was the unclaimed amorphous cabozantinib (L)-malate that behaved unexpectedly, dissolving anomalously slowly. DFF ¶ 221. Dr. Steed's testimony is corroborated by Exelixis's own conclusions from 2014, when dissolution studies showed that amorphous cabozantinib "in contact with aqueous media tended to form gel-like clumps that . . . are very slow to dissolve," and that "chunks of undissolved material (gel-like lumps) were found in the amorphous material." DFF ¶ 222. Thus, any "improved" dissolution of the crystalline over amorphous forms is a function of the poor dissolution of the amorphous material, not any unexpected or superior property of the claimed invention.

F. Exelixis has not shown that the compositions of claim 3 of the '349 patent produced unexpected results.

Exelixis provided no expert testimony that the claimed compositions produced unexpected results. DFF ¶ 224. Although Dr. Shah testified that capsules and tablets of cabozantinib (L)-malate remained essentially free of the 1-1 impurity even after manufacture and storage, Dr. MacMillan testified that these results were expected because cabozantinib (L)-malate is "very stable." DFF ¶ 192. Dr. Donovan agreed—a POSA would have expected that the API could be formulated into a capsule or tablet and remain essentially free of the 1-1 impurity. DFF ¶ 225.

VII. CONCLUSION

The Court should find that all of the asserted claims are invalid.

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